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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,589	01/15/2004	Keizo Koya	3211.1001-001	5403

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
07/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,589	KOYA ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-14,16,17,25-31,33-35 and 37-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-14,16,17,25-31,33-35,37,39,43,46,47 and 50* is/are rejected.

7)☒ Claim(s) *38,40-42,44,45,48 and 49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/18/2008 and 5/1/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 8-14, 16-17, 25-31, 33-35, and 37-50 are presented for examination

Applicants' amendment filed 3/18/2008 has been received and entered into the application. Accordingly, claims 8, 11-13, 16, 25, 28-30, 33-35, and 37-39 have been amended, claims 40-50 have been added, and claims 1-7, 15, 18-24, and 32 have been cancelled.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

In light of the new rejection (Obviousness Type Double Patenting) being applied against the pending claims, this Office Action is **Non-Final**.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statements filed 3/18/2008 and 5/1/2008. The Examiner has considered the references cited therein to the extent that each is a proper citation. The "Remarks" paper as submitted by Applicants' representative was not considered because it is not a published document. If Applicants want the data presented in this paper to be considered, the Examiner suggests filing the data in a 37 CFR 1.132 Declaration. Please see the attached USPTO Form 1449.

Response to Arguments

Applicant's arguments filed 3/18/2008 have been fully considered but they are not persuasive. With respect to the 35 U.S.C. 112, 1st Paragraph rejection, in the Interview conducted on January 29, 2008, the Examiner indicated that claims limited to R_1 and R_2 substituents that are substituted or unsubstituted phenyl groups would overcome this rejection. Applicants argue that they have amended the claims meet the Enablement requirement as agreed in the interview. However, claim 13-14 and 30-31 recite methods encompassing administration of compounds wherein R_1 and R_2 are both a substituted or unsubstituted "aliphatic group", which is much broader than "phenyl group" as discussed in the interview. There are only two examples of compounds (compounds 17 and 18) having a substituted or unsubstituted aliphatic group, and in both cases the aliphatic group is cyclopropyl. Accordingly, claims 13-14 and 30-31 remain rejected for the reasons of record and as reiterated below.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-14 and 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment methods comprising administering a compound wherein R_1 and R_2 are both cyclopropyl or 1-methylcyclopropyl, does not reasonably provide enablement for treatment methods comprising administering a compound wherein R_1 and R_2 are other substituted or unsubstituted aliphatic groups. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

6) the relative skill of those in the art,

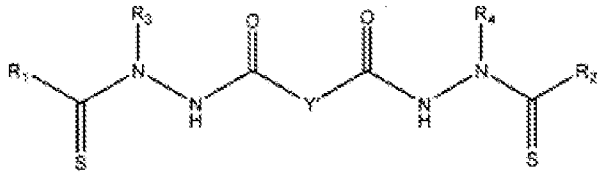
7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to treating a subject having cancer or a multi-drug resistant cancer selected from the group consisting of leukemia, uterine sarcoma, and melanoma, comprising administering an effective amount of a compound represented by the following structural formula:



wherein R_1 and R_2 are both a substituted or unsubstituted aliphatic group.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art, the examiner cites Sausville *et al.* (Cancer Research, 2006, vol. 66, pages 3351-3354) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Sausville *et al.*, cited for evidentiary purposes, teaches that traditionally explored tumor model systems are insufficient to predict how actual human beings will respond to treatment in the clinic (page 3351, left column). Even when drugs with evidence of anticancer activity in preclinical *in vivo* models are given their maximum tolerated dose in humans, they frequently fail to produce useful activity in humans (*id.*). Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In*

re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers.

2. The breadth of the claims

The claims are extremely broad insofar as they disclose the general treatment of leukemias, uterine sarcomas, or melanomas and multi-drug resistant leukemias, uterine sarcomas, or melanomas by administering to a subject a compound as defined in the claims.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat all of the various cancers claimed, particularly in humans.

The direction concerning treating cancer is found in the specification at pages 79-94, which provides *in vitro* cellular assays and *in vivo* assays for determining the cell growth inhibitory effect of the claimed compounds. In this regard, compound **1** (page 80) was shown to inhibit the growth of a myeloid leukemia cell line (HL-60), a uterine sarcoma cell line (MES-SA), and a melanoma cell line (Bowes/OV2) *in vitro*. Compounds **2-18** were shown to inhibit

the growth of the multi-drug resistant uterine sarcoma cell line, MES-SA/DX5, *in vitro* (Table 2). It is noted that all of these compounds have similar substitutions (*e.g.*, in all cases, Y is CH_2 and R_5 and R_6 are H, and in the majority of compounds R_1 and R_2 are unsubstituted or substituted phenyl and R_3 and R_4 are methyl, ethyl, or phenyl). The only working examples of the claimed compounds wherein R_1 and R_2 are both a substituted or unsubstituted aliphatic group are compounds 17 and 18, wherein R_1 and R_2 are both 1-methylcyclopropyl or cyclopropyl, respectively. A compound structurally similar to compound **1** (compound **16**) was shown to have *in vivo* activity against a multi-drug resistant uterine carcinoma in nude mice at a dose of 15 mg/kg (Example 17). Compound **1** also was shown to inhibit leukemia cell growth *in vitro* (Example 19) and *in vivo* (Example 20). Thus, out of the plethora of possible compounds having a substituted or unsubstituted aliphatic group asencompassed by the claims, only two such compounds (compounds **17** and **18**) were tested *in vitro* (against a multi-drug resistant uterine sarcoma).

Applicants describe formulations at pages 22-23. Doses required to practice their invention are also described at pages 22-23. In this regard, Applicants disclose that "an effective amount" of the claimed compounds is the quantity of compound in which "a beneficial clinical outcome is achieved when the compound is administered to a subject with a cancer" (page 22, lines 26-28). A 10,000-fold range of doses is recommended (*e.g.*, 1 mg to 10 g/mm^2 per day)^2.

Since only two structurally related compounds of the invention have been shown to be effective against MES-SA/DX5 cells (a multi-drug resistant uterine sarcoma cell line) *in vitro* (Table 2), how is the skilled physician to know what dose to administer to a subject for each of

the pathologically different cancers and structurally diverse compounds encompassed by the claims? There are no guidelines for determining the doses needed to treat a carcinoma *vs.* a myeloid disorder *vs.* adenoma *vs.* leukemia. Are the identical doses to be used for treating these unrelated cancers? Further, Applicants provide minimal guidance on how one skilled in the art can make the plethora of structurally divergent compounds encompassed by the claims.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the full scope of the instantly claimed genera of compounds could be predictably used as a treatment for cancer as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because two compounds as recited in the claims inhibit uterine sarcoma cell proliferation *in vitro*, the plethora of structurally divergent compounds encompassed by the claims must therefore, *a priori*, be useful in the treatment of cancerous cell growth. However, the claims encompass a multitude of compounds (literally millions) having a plethora of chemically and biologically distinct

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[2] It is noted that the "mm^2" appears to be a typo as m^2 is traditionally used to refer to doses. For example, an average human has a surface area of about 2 m^2.

substituents. Accordingly, the evidence of biological activity presented in the specification is not seen as commensurate in scope with the patent protection sought by Applicants. Further, it would take undue experimentation to determine exactly what compounds encompassed by the claims will have efficacy against any given cancer in a subject.

In this regard, the law requires that disclosure in an application shall inform those skilled in the art how to use Applicant's invention, not how to find out how to use for themselves. Applicants say that their invention is in the discovery of a novel class of anticancer compounds. They are not claiming the compounds *per se*. There are three consecutive paragraphs (pages 22-23) of the specification and one specific example (page 93, Example 20) collectively relating to dosage and administration techniques which may be summarized as saying that the compounds can be administered in all the usual ways, as solids, solutions, and suspensions; in capsules, tablets, or suspensions; to be administered orally, parenterally, by inhalation, or rectally; and the carrier may include any suitable pharmaceutically acceptable carrier. Whatever the nature of the dosage unit, it may be administered in a range of 1 mg/mm^2 [m^2] per day to about 10 grams/mm^2 [m^2] per day. The "effective dose" as instantly claimed appears to mean that somewhere in the above dose range, an anticancer effect in a subject will be achieved. However, Applicants do not say at what point in the process of administering to a patient, say a 10 mg capsule, an anticancer effect may be expected in the course of proceeding at some unspecified intervals toward a possible 500th capsule for the day (*i.e.*, a total of 5 grams/day for an average human). Nor do the Applicants suggest whether in might be better to start off with a 10 mg capsule, a 50 mg tablet or a 150 mg bolus injection.

This uncertainty, particularly when coupled to the fact that the claims encompass millions of possible compounds, which, in turn, is coupled to the fact that the subject being treated is not necessarily a human being, amounts to a failure to comply with the requirements of 35 U.S.C. 112, 1st Paragraph. In effect, Applicants have said to those skilled in the art: Here is a group of new compounds, two of which have been shown by us to have anticancer activity *in vitro* against one cell line; you can put any of them up in convenient dosage units and you can try them out on human patients or animal subjects as you wish and somewhere along the line, for any given compound in any given cancer, from a dose of 1 mg/m^2 per day to 10 $grams/m^2$ per day, you will probably achieve an anticancer effect in a subject.

In other words, those skilled in the art, by investigations along the above lines, and by a great amount of work, can eventually find out how to use the Applicants' invention to treat cancers in subjects by administering one of the millions of compounds encompassed by the claims. It is evident that a very small percentage of the claimed compounds were actually synthesized and tested by Applicants and the two compounds tested *in vivo* are not encompassed by the rejected claims. In other words, the structure activity relationship demonstrated in the examples is limited to a very small sub-genus of compounds.

Determining if any particular claimed compound would treat any particular cancerous disease state would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants. Further, as noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

USP No. 7,385,084

Claims 8-14, 16-17, 25-31, 33-35, 37, 39, 43, 46-47, and 50 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 24-29 and 32-34 of U.S. Patent No. 7,385,084. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of the '084 patent encompass administration of salts of the compounds instantly claimed to treat melanoma. As such, it would have been obvious to one of ordinary skill in the art that the salts as claimed in the '084 patent

are reasonably a "pharmaceutically acceptable salt" of the compounds recited in the instant claims.

Allowable Subject Matter

Claims 38, 40-42, 44-45, and 48-49 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614